REMARKS

Prior to the Office Action mailed October 10, 2001, claims 19-25 were pending. Claims 19, 20, 22, and 24 have been withdrawn, although, as set forth below, Applicants maintain that upon a finding of allowability of claim 25, claim 19 should be rejoined. Upon entry of this amendment, claims 21, 23, 25, 26, and 27 will be active and pending in this case. Support for new claims 26 and 27 can be found in the specification in Example 1, page 50, lines 1-14, and thus do not constitute new matter.

The Examiner noted that Applicants probably inadvertently recited group III, instead of group II in stating that upon a finding of allowability of claim 25, rejoinder of claim 19 with the other claims of group III is mandated by MPEP §821.4 and U.S. Patent and Trademark Office Procedure, as discussed in the Amendment and Request for Reconsideration filed November 30, 2000. Applicants thank the Examiner for bringing this error to light, and acknowledge that it was group II that was intended. Applicants maintain that rejoinder is proper in this case.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, NEW MATTER, AND SECOND PARAGRAPH, INDEFINITENESS

The Examiner has rejected claims 21, 23 and 25 under 35 U.S.C. §112, second paragraph, as indefinite. Specifically, the Examiner alleges that pending claim 25 is confusing with regard to whether the polypeptide encoded by the DNA sequence in item d) is bound to the active compound of b) via a peptide bond, besides being bound to the active compound of b) via the cleavable amino acid sequence of c) or whether the polypeptide encoded by the DNA sequence in item d) is bound to active compound of b) via a peptide bond of the cleavable amino acid sequence of c).

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The Examiner also has rejected claims 21, 23 and 25 under 35 U.S.C. §112, first paragraph, for lack of written description and lack of enablement. According to the Examiner, the specification fails to describe the linkage of component d) to component b), the term "by a peptide bond".

Without acquiescing in these rejections, applicants have obviated the rejections by amending claim 25 as set forth above. This amendment solely serves to clarify what was evident from the claim language of claim 25 from the beginning: the three compounds, i.e., the active compound encoded by the nucleic acid of b), the cleavable amino acid sequence encoded by the nucleic acid of c) and the inhibitory polypeptide encoded by the nucleic acid sequence of d) of the polypeptide according to claim 25 are comprised within a single polypeptide, and thus linked to each other by peptide bonds, wherein the inhibitory polypeptide encoded by the DNA sequence in item d) is bound to the active compound according to item b) via the cleavable amino acid sequence of item c). The fact, that the three compounds are comprised within a polypeptide (and thus linked by peptide bonds) is disclosed in the specification, inter alia, at page 4, lines 13 to 31, at page 9, lines 6 & 7, in Figure 1 (particularly "Protein BCD, encoded by the structural gene"), at page 9, lines 28 to 30, and at page 12, lines 14 & 15. The arrangement of the three compounds within the polypeptide according to claim 25 (with the inhibitory polypeptide encoded by the DNA sequence in item d) being bound to the active compound according to item b) via the cleavable amino acid sequence of item c)) can be found at page 4, lines 13 to 31, in Figure 1, and at page 15, lines 30 to 35 of the specification.

REJECTION UNDER 35 U.S.C. §101/§112, FIRST PARAGRAPH

The Examiner maintains the rejection of claims 21, 23 and 25 under 35 U.S.C. §112, first paragraph, for lack of credible and specific utility. Applicants respectfully

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traverse this rejection because it is based upon an improper legal standard. However, applicants further respond by rebutting the Examiner's assertion with evidence in the form of written attestations from Roland Kontermann, Ph.D., one of skill in the art of the invention. In the attached rule 132 Declaration, Dr. Kontermann provides a reasoned analysis of the invention and the state of the art at the time of filing, and concludes that uses for the invention were immediately apparent at the time of filing.

In support of the rejection, the Examiner asserts that:

> ...since Denmeade et al teach that the prodrug activation *in vivo* and tumor cell killing *in vivo* are to be tested and evaluated, and in view of the unpredictability of cancer treatment, as overwhelmingly evidenced by Gura et al, Jain et al, Curti et al, and Hartwell et al (of record), one of skill in the art would have expected that the claimed *in vivo* prodrug activation and tumor cell killing are unpredictable. Further, although PSA is enzymatically active in extracellular fluid, once in serum, PSA [has] no assayable enzymatic activity (Denmeade et al, p.4929, second column, first paragraph), and thus it is unpredictable whether PSA has any assayable enzymatic activity in the serum even for a short time, unless tested

Page 8, lines 5-8, (emphasis added)

Under the law, an applicant's asserted utility is presumed valid. The standard for overcoming this presumption is not whether one of skill in the art would find the asserted utility unpredictable, but whether it is more probable than not that one of skill in the art would doubt the truth of the statement of utility. MPEP (8th Ed.) §2107.02(III)(A). The fact that Denmeade et al speculates as to whether a peptide could be used as a carrier to target products for activation within sites of metastatic prostate cancer producing

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enzymatic active PSA actually supports the asserted utility. That is, Denmeade et al are skilled artisans and although they acknowledge that the hypothesis needs to be tested, this "speculation" at minimum suggests that the authors believe the asserted utility may be true. The Examiner has not demonstrated by a preponderance of the totality of the evidence that one of skill in the art would doubt the truth of the statement of utility. As noted earlier, courts have generally only sustained utility rejections where "the applicant failed to disclose any utility or asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." MPEP §2107.02(III)(B). The utility asserted in this case violates no such principle and as evidenced by Denmeade et al, is not wholly inconsistent with contemporary knowledge in the art.

The Examiner further asserts that because Denmeade et al disclosed that different substrate peptides for PSA have different levels of stability in various sera, "[i]t is unpredictable that the claimed substrate peptide Arg-Lys-Tyr for PSA is stable *in vivo*." The above arguments apply equally to this assertion. Unpredictability of *in vivo* stability is not an appropriate basis for rejection of the claim. The Applicant has asserted a utility, and it is the burden of the Examiner to show by a preponderance of evidence, not speculation, that the utility is not credible. There has been no evidence cited to show that the claimed substrate peptide is unstable *in vivo* or that one of skill in the art would believe it to be so.

The Examiner further asserts at page 8 that "since Applicant has not shown the utility of the claimed construct, it is Applicant's burden to provide guidance on the issues such as factors that could potentially have an adverse effect on successful therapy, including biological stability, half-life, clearance from the blood, degradation, immunological activation, inability to penetrate tissues or cells, absorption, and insufficient circulation in the target area to carry the formulation in appropriate

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concentrations." Applicants respectfully disagree. Applicants have asserted a specific utility for the invention. A biological effect, initiation of coagulation, has been identified and it has a reasonable correlation with the asserted utility of depriving a tumor of blood flow. This is all that is required under relevant law, as set forth in MPEP §2107.02(II)(A). Applicants have met their burden.

At page 9 of the Office Action, the Examiner disputes the correlation between the *in vitro* data and the *in vivo* utility. The Examiner asserts "there is no correlation between *in vitro* assays and *in vivo* treatment in the instant application. Applicant however, has shown only that in *in vitro* conditions, transduced HEK 293 cells express mutated factor X, which in the added presence of PSA, counterbalances the coagulation defect of FX-deficient plasma. There is no disclosure of *in vivo* tumor treatment."

In response, applicants argue that a correlation between the *in vitro* data and the asserted *in vivo* use, does in fact exist under the relevant legal standard. The Federal Circuit, in Cross v. Iizuka, 753 F.2d 1040, 1051, 224 USPQ 739, 747-48 (Fed. Cir. 1985), commented on the significance of data from *in vitro* testing that showed pharmacological activity:

> "We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort of further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility."

MPEP (8th Ed.) §2107.01(III).

Here, the *in vitro* data is such a first link. The *in vitro* study acknowledged by the Examiner demonstrates pharmacological activity of the claimed construct. This pharmacological activity relates to the coagulation of blood. At the time of the invention,

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it was well known to the skilled artisan that tumors require blood in order to grown. Therefore, an invention that interferes with such blood flow, could be useful for the treatment of such tumors.

This explanation also is relevant to counter the Examiner's contention that because treatment of cancer is unpredictable, more detail is needed in the specification to enable one of skill in the art to make and use the invention, and that the specification lacks guidance on necessary dosages and treatment schedules for successful using of the claimed constructs in the *in vivo* treatment of cancer. Applicants respectfully point out that Example 2 discloses a construct that encodes a mutated factor X which cleaves in the presence of PSA and initiates coagulation. Thus, the construct is not intended to destroy the tumor by directly counteracting the nature of the cancer, but through coagulation and depriving the tumor of blood flow. In contrast to the "treatment of cancer," the coagulation pathway is very well known in the art, and has a far greater degree of predictability, and therefore requires less information to be explicitly stated in the specification under MPEP 2164.03.

The Examiner states that "[c]oncerning the alternative means of survival of tumors, since it is unpredictable that the claimed compound could be used for treating cancer, it is even more unpredictable that there exists a second, non-claimed compound that would work in synergy with the claimed construct." Applicants wish to clarify the argument made in the previous reply. The Examiner had suggested that even if the invention were to work as claimed, it would lack utility if the target cell had an alternative means of survival. Applicants traverse this assertion on the basis that an alternative means of survival is not dispositive on the issue of utility. Even if the claimed construct is only effective for disrupting one means of survival, that is a useful result. If another means of survival does exist, then there may also be another compound that would be effective at counteracting that means. If so, then that second compound would

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have its own separate utility. But, whether that second compound exists or not, or even whether a second means of survival exists or not, is irrelevant to the issue of whether the claimed construct is useful. If the claimed compound is effective at initializing coagulation in the proximity of a tumor, for example, then that is a sufficient specific utility. Many therapies require the use of multiple compounds or treatment means. Radiation and chemotherapy, for example, are often administered in combination in successful cancer treatment. Surely, the fact that both are necessary does not negate the utility of either method alone.

The Declaratory evidence from Dr. Kontermann supports all of the above arguments and explanations . In Section II., Dr. Kontermann describes the work of Watt *et al.,PNAS USA* 83: 3166-3170 (1986) involving mutated Factor X and how *in vitro* studies were predictive of success. He explains how the methods of the invention are preferable over traditional therapeutics and how the treatment of tumors through targeting blood vasculature rather than the tumor cells is scientifically accepted. Dr. Kontermann supports his contentions with scientific literature, copies of which are attached and listed on Form 1449, for the Examiner's convenience.

In summary, the specification asserts a specific utility for the claimed polypeptide which is presumed credible and further shown to be credible in view of the teaching of the specification itself, in view of the publications of record, and in view of further evidence in the form of the §1.132 Declaration of Dr. Kontermann and the references relied upon therein. Accordingly, Applicant respectfully requests that the rejection of claims 21, 23 and 25 under 35 U.S.C. §101/§112 be withdrawn.

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REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, ENABLEMENT

The Examiner rejects claims 21, 23, and 25 under 35 U.S.C. §112, first paragraph, as lacking enablement, for the reasons of record in paper No. 11. As the reasons set forth for this rejection are the same as those under the section §101 argument in the pending Office Action, Applicants maintain that with the withdrawal of the rejection of claims 21, 23 and 25 under section §101, the rejection of those claims under section §112, first paragraph for lack of enablement should also be withdrawn.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, SCOPE

The Examiner has rejected claims 21, 23 and 25 under 35 U.S.C. §112, first paragraph, for lack of enablement commensurate in scope with the claims. Particularly, the Examiner asserts that a polypeptide construct comprising an amino acid sequence cleavable by any protease released from any mammalian cells would be cleaved in the serum by proteases such as trypsin or chymotrypsin etc., before reaching the target cells, and thus would be useless. Applicants respectfully disagree with the Examiners position.

Without acquiescing in this rejection, applicants have obviated the rejection by amending claim 25 as set forth above. This amendment solely serves to clarify what was evident from the claim language of claim 25 from the beginning: The cleavable amino acid sequence of c) is not to be cleaved by any protease but specifically by a protease that is released at or from a mammalian target cell. The fact, that the protease can be released from or at a target cell, is disclosed in the specification, inter alia, at page 3, line 14 and lines 20-25, page 9, line 32 ff., page 10, lines 11-15, page 15, line 36 - page 16, line 1, and page 39, lines 11 and 12. For example, page 10, lines 20-21 of the specification discloses the proteases to be "formed in tumors of secreted by tumor cells or inflammatory cells". Page 3, lines 13 to 22 of the specification discloses a "target cell-specific therapy for tumors and inflammations", that uses the "secretion of enzymes in

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tumors or areas of inflammation". This means, that e.g. tumor cells can be targeted by using the release of proteases by the tumor cells or in the tumor and that inflammatory cells can be targeted by usage of proteases released by the inflammatory cells or in the inflammatory area. Understanding from pages 34 to 38 of the specification relating to different embodiments of the active compound such as nerve growth factors (page 37, lines 18 ff.) or proteins lowering the blood pressure (page 37, lines 33 ff.), that the invention is not restricted to the targeting of tumors and inflammations, the skilled artisan reads the above-indicated passages as disclosing a release of the protease at or from the target cell.

Moreover, the polypeptide according to claim 25 can be administered to the organism in different ways, such as by local or systemic delivery. Nevertheless, application of the polypeptide according to the invention is not restricted to systemic administration. For instance, the treatment of inflammatory diseases or wounds e.g. a local administration onto affected areas of the skin (e.g., as a paste of powder) would physically restrict the spatial distribution of the polypeptide. Choosing the right type of administration and formulation (e.g. as a paste, spray or powder in contrast to injectable solutions) was well within the ordinary skill of a skilled artisan at the time of the invention and the practice of the invention would constitute no undue burden. The artisan would have been aware of the right choice of application in order to prevent side effects or enhance the therapeutic effect of therapeutic substances. Moreover, applicants respectfully disagree with the Examiner's assertion that possible protease-substrate couples are not disclosed by the specification: Paragraph 3 on page 39 of the specification lists several publications on this subject, which are incorporated by reference.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, SCOPE, NEW REJECTION

The Examiner rejects claims 21, 23 and 25 under 35 U.S.C. §112, first paragraph, stating that the specification is only enabling for a polypeptide encoded by a nucleic acid construct, comprising at least one DNA sequence encoding a polypeptide, which is bound to an active compound via an amino acid sequence cleavable by a protease, and inhibits the activity of said active compound, wherein the inhibiting polypeptide and active compound are a prepro-protein, and wherein the nucleic acid encoding the cleavable amino acid sequence does not naturally occur as operably linking the inhibiting nucleic acid sequence to the nucleic acid sequence encoding the active compound.

More specifically, the Examiner argues that it is not clear how the inhibition of the activity of an enzyme, which is inhibited by an enzyme inhibitor, is abolished upon cleavage of a linker, wherein the enzyme and the inhibitor are linked by a peptide linker, explaining that enzyme inhibitors tightly bind to the inhibited enzyme. Applicants respectfully disagree with this position.

Claim 25 is directed to a polypeptide encoded by a nucleic acid construct, comprising at least one DNA sequence encoding a polypeptide, which is bound to an active compound via an amino acid sequence cleavable by a protease, and inhibits the activity of said active compound, and wherein the nucleic acid encoding the cleavable amino acid sequence does not naturally occur as operably linking the inhibiting nucleic acid sequence to the nucleic acid sequence encoding the active compound. Neither the claim language nor the specification require the polypeptide of the invention to be limited to polypeptides wherein the inhibitory polypeptide and the active compound are prepro-protein. The term "prepro-protein" is commonly employed for proteins undergoing more than one step of proteolytic processing (such as, *e.g.*, secreted protein precursors, that undergo proteolytic cleavage of the amino-terminal secretion signal

peptide followed by further proteolytic processing in the extracellular compartment). Clearly, a polypeptide according to the invention, wherein the inhibiting polypeptide and active compound are a prepro-protein constitutes an example, as far as the secretion of the polypeptide is desired. Yet, since *in vitro* protein expression and purification are routine techniques for a person skilled in the art, it is clear that the polypeptide according to the invention need not necessarily be purified from the supernatant of the producing cells, but can also be purified from cell extracts. Therefore, the inhibiting polypeptide and active compound need not necessarily form a prepro-protein, but can also form *e.g.*, a pro-protein. Yet, these are not this only types of proteins enabled by the specification. As disclosed by the specification, page 15, line 4 ff., the inhibitory polypeptide of item d) can be encoded by "any arbitrary nucleic" acid, as long as it exerts its inhibitory function when bound to active compound b) via cleavable amino acid sequence c). Thus, active compound and inhibitor need not necessarily form a prepro-protein.

The Examiner states that enzyme inhibitors necessarily bind so tightly to the inhibited enzyme that even after the cleavage of cleavable amino acid sequence c), they will not dissociate from the enzyme. However, the specification does not disclose the sole use of this type of enzyme inhibitor. As is generally known to those skilled in the art, enzyme inhibition is (among other factors) dependent of the relative concentrations of enzyme and inhibitor as well of the affinity of the inhibitor for the enzyme. By choosing an inhibitor with moderate or low affinity for the active compound, the inhibitor will inhibit the active compound when held in close proximity (which means a constantly high local concentration of inhibitor) by means of the linkage to the active compound via the cleavable amino acid c). After cleavage of the cleavable amino acid sequence, the low affinity inhibitor is free to dissociate from the enzyme-inhibitor complex setting free the active compound, which then can exert its function. Thus, when using inhibitory components with a moderate to low affinity for the enzyme, one of skill in the art will expect the active compound to be activated (especially, if the inhibitor is not an

endogenous inhibitor, and thus not present in the organism, or is an endogenous inhibitor, which is not present at the site of cleavage of the cleavable amino acid c), or only present in a low concentration). These functional relations are routine knowledge for one with skill the art. The skilled artisan only needs to choose suitable components as outlined above in order to construct a polypeptide according to the invention that is not a prepro-protein. Therefore, no undue experimentation is required to practice the full breadth of the claimed invention.

CONCLUSION

In view of the above amendment, arguments and declaratory evidence with supporting documentation, Applicants request the withdrawal of all rejections of the pending claims. Applicants further assert that this application is in condition for allowance, and respectfully request rejoinder of claim 19 with the other claims of group II in accordance with MPEP §821.4 and U.S. Patent and Trademark Office Procedure.

Respectfully submitted,

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Date

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